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Biomedical Applications of Stochastic Processes*,**

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PURDUE UNIVERSITY

DEPARTMENT OF STATISTICS

DIVISION OF MATHEMATICAL SCIENCES

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Mimeo series 370.

Department of Statistics
Division of Mathematical Sciences
Mimeograph Series #370

June 1974

*To appear in the Proceedings of the American Mathematical Heritage (Bicentennial) Symposium on the History of Statistics and Probability, held during May 27-29, 1974, at Southern Methodist University, Dallas, Texas.

**This research was supported by the Office of Naval Research under Contract N00014-67-A-0226-00014 and Air Force Contract AFOSR-72-2350 at Purdue University.

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER
Mimeograph Series #370

2. GOVT ACCESSION NO.

3. RECIPIENT'S CATALOG NUMBER

4. TITLE (and Subtitle)
Biomedical Applications of Stochastic Processes

5. TYPE OF REPORT & PERIOD COVERED
Technical

6. PERFORMING ORG. REPORT NUMBER
Mimeo Series #370

7. AUTHOR(s)
Prem S. Puri

8. CONTRACT OR GRANT NUMBER(s)
N00014-67-A-0226-00014
AFOSR-72-2350

9. PERFORMING ORGANIZATION NAME AND ADDRESS
Purdue University
W. Lafayette, IN

10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
00014

11. CONTROLLING OFFICE NAME AND ADDRESS
Office of Naval Research
Washington, DC

12. REPORT DATE
June 1974

13. NUMBER OF PAGES
22

14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)

15. SECURITY CLASS. (of this report)

15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)
Distribution of this document is unlimited.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)
Biology; Health; Medicine; Stochastic Models, Stochastic Processes; Branching Processes, Birth and Death Processes; Emigration-Immigration Processes; Semi-Markov Processes; Renewal Processes, Diffusion Processes; Quantal Response Processes; Competition Processes.

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)
This is a nonmathematical paper intended for sophisticated but otherwise nonmathematical readers. The paper starts with the emphasis on stochastic models in Biology and Medicine which, because of the large variability among observations in these areas, are considered more appropriate than their deterministic analogs. Again, owing to the basic evolutionary characteristics of living things such as births and deaths, growth and decay etc., one is led in biology and medicine to many dynamic processes of development in time and space. Consequently, the use of stochastic processes for model-building for the study

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

Unclassified
SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

of various biological phenomena becomes quite natural. The paper attempts to describe nonmathematically some of the special processes, which have emerged as useful models in biology and medicine over a period of time. Among others, the processes considered here are Branching processes, Birth and Death processes, Emigration-Immigration processes, Diffusion processes, Competition processes, etc. In each case a brief sketch, frequently historical in character, is followed by a few examples of live situations where these processes arise in practice. The paper ends with about one hundred references of key papers concerning these processes, to which the reader is referred to for further details, both about their applications and their theoretical developments.

Biomedical Applications of Stochastic Processes*

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Prem S. Puri
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1 INTRODUCTION. It is well recognized that in the biological and medical sciences, variability among the observations is much larger, more fundamental and intrinsic than in some other disciplines such as Physics, where it is often possible (although not always) to dispose of a major part of the variability by controlling certain relevant factors in the laboratory. This variability in turn makes the stochastic models much more appropriate in biology and medicine than their deterministic analogs. Again the basic evolutionary characteristics of living things such as births and deaths, growth and decay, change and transformation, lead us in biology and medicine to many dynamic processes of development in time and space. Thus one is led to the use of the so called stochastic processes as a natural vehical for stochastic model-building for the study of various biological phenomena.

In short, a random phenomenon that arises through a process which is developing in time or in space in a manner controlled by probabilistic laws is called a Stochastic process. The examples are many, for instance, the growth of a population such as a bacterial colony; the spatial distribution of plants and animal communities; spread of an epidemic; spread of cancer growth within the body; and so on. Mathematically a stochastic process is defined as a collection $\{X(t), t \in T\}$ of random variables indexed by a parameter t, which takes values over an index set T of the process.

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*This research was supported by the Office of Naval Research under Contract N00014-67-A-0226-00014 and Air Force Contract AFOSR-72-[illegible]50 at Purdue University. Reproduction in whole or in part is permitted for any purpose of the United States Government.

Typically either the set T consists of nonnegative integers, or T is the nonnegative half of the real line i.e. $[0,\infty)$. In the first case the collection can be rewritten as $\{X_n, n = 0,1,2,\ldots\}$, the so called discrete (time) parameter process. The second case $\{X(t), t \geq 0\}$ is called the continuous (time) parameter process. In practice, the discrete time case arises for instance when X_n represents the number of progeny in the nth generation of the growth of a tribe. In the continuous time case, $X(t)$ may represent the number of patients in a hospital present at time t, and so on.

In the following sections we describe briefly some of the key stochastic processes, which have been commonly used as stochastic models suitable for many of the biological phenomena. In each case a brief sketch is followed by a few examples of the live situations where these processes arise in practice. However it is only fair to add the following remarks at this point for the sake of the reader. The author could have selected for the following presentation the various stochastic processes according to their classical properties such as Markov or nonMarkov, stationary or nonstationary, etc. However such classifications appeared too broad for our purpose here. Instead, it was felt appropriate to mention only the 'special processes', which have emerged in their own right as useful models in biology and medicine. Of course, even within this limited scope, the author does not claim the present account to be either complete or exhaustive in touching the various milestones in this area of biomedical applications of stochastic processes. A similar remark applies to the reference list (given at the end of the paper) of the various contributors in this area. Also it should not be taken to mean that the broad classifications mentioned above had in anyway less influence on the study of various live phenomena. In fact these classifications are natural, when one embarks on a theoretical investigation of the stochastic processes.

The reader may find an excellent account of such investigations in treatises such as by Doob [17], Dynkin [19], and Feller [28], [29]. In particular, in the last two references by Feller, the reader may find a colorful and rich account of probability, both theory and its applications. Another two-volume treatise, recently published, is due to Iosifescu and Tăutu [45]. Here the authors devote the first volume to the theory of stochastic processes and the second volume entirely to its applications in biology and medicine.

2 BRANCHING PROCESSES. An important class of processes arising in many live situations is what is commonly known as Branching Processes, a term which appears to have been introduced in 1947 by the Russian mathematicians A. N. Kolmogorov and N. A. Dmitriev [62]. Historically these processes go back one hundred years ago to Francis Galton, a British biometrician. Galton was interested in 1870s in the decay of families of men who occupied conspicuous positions in the past. The question raised was whether this extinction of family names was merely a chance phenomenon or in fact whether the physical comfort and intellectual capacity were necessarily accompanied by a decrease in fertility. In 1873, Galton [33] posed the following problem, which appeared as problem #4001 in Educational Times, a mathematical periodical then published in London.

Problem 4001: A large nation, of whom we will only concern ourselves with adult males, N in number, and who each bear separate surnames, colonize a district. Their law of population is such that, in each generation, a_0 per cent of the adult males have no male children who reach adult life; a_1 per cent have one such child; a_2 have two, and so on. Find (1) what proportion of the surnames will have become extinct after r generations; and (2) how many instances there will be of the same surname being held by m persons. (In Galton's case, the number of possible positive a_i's went as far as five, but this is a minor point).

After some persuasion by Galton, Henry William Watson, a clergyman and a mathematician, attacked this problem. The underlying discrete time stochastic process as described here is now commonly known after their names as Galton-Watson process (G-W process for short). Watson [98] showed that if q is the probability of a family name ultimately becoming extinct, then this probability must satisfy the equation $x = \sum_{k=0} a_k x^k$, where of course $\sum_{i=0} a_i = 1$. And since $x = 1$ is a solution of this equation, Watson thus concluded from this, that the probability of ultimate extinction is always one, no matter what the probabilities $a_0, a_1, a_2, \ldots$ are. What he failed to notice was that under certain conditions on a_i's, there are two solutions of the above equation lying between 0 and 1 and that it was smaller of the two, which was the correct answer. Anyway, it took another about sixty years before the problem was completely solved by J. F. Steffenson in 1930 (see [93], [94]). The solution he gave is the following:

If $a_1 \neq 100$ per cent, then the probability of ultimate extinction of a given family name is one if the <u>average</u> number of sons of the type mentioned, born per male parent is no more than one; and this extinction probability is strictly less than one if this average number is greater than one. As it turned out, the later investigations showed that the detailed behavior of these processes varies according to whether the average number of sons is less than one, the so called subcritical case; is equal to one, the critical case; or is greater than one, the supercritical case.

There is of course much more history behind all this and instead the reader is referred to a paper by Kendall [56], where he has given an excellent chronological account of the early history of these processes.

After 1940, interest in the branching process model increased along with the interest in the applications of probability theory and also of course

because of its analogy between the growth of families and the nuclear chain reactions. Several other aspects of the Galton-Watson problem were studied during 1940-50. Also the original process was generalized in many directions inspired by various live situations. Particular reference should be made here to the works of Hawkins and Ulam [41], Harris [37], [38], Everett and Ulam [20], [21], Bellman and Harris [8], [9] and Otter [75], all in the United States, and of Kolmogorov and Dmitriev [62], Yaglom [101], Kolmogorov and Sevast'yanov [63] and Sevast'yanov [85], [86], [87], [88], in the Soviet Union. Again the G-W process as defined above is a Markov process. The Markov processes in simple terms are defined as those processes, where the future probabilistic course of the process depends only on the present state the process is in and not on the past history of the process. Thus a non-Markovian generalization of a continuous time analog of G-W processes was developed in 1948 by Bellman and Harris [8], the so called Bellman-Harris age-dependent branching processes, although a special case of these was already studied as early as 1939 by Feller [22]. In analogy with cell growth, here an individual lives for a random length of time and then at death is replaced by a random number of progeny; the basic feature of the branching processes as always being that each individual, independent of the other individuals, undergoes the same chance process, under the same probability laws as did its parent. Another generalization of the original G-W process was developed and studied by Everett and Ulam [20], [21] in 1948, and is called the Multi-type Galton-Watson processes, which were later generalized further to the age-dependent multitype branching processes. Here an individual could give offspring not only of its own type but of other types as well. An example, for instance is in cell populations, where some of the progeny at birth may undergo mutation, yielding mutant types, different from the normal 'wild' type.

In 1963, came out the book on branching processes by Harris [40], giving a complete account of these processes until about that time. This book served as a great stimulus for further research both in theory and in applications of these processes. Meanwhile the work became so much in volume that since then three more books have come out on the subject, one by Mode [68], and another by Athreya and Ney [1], both in the United States, and finally the third in Russian by Sevast'yanov [89], who along with his students have contributed considerably on the subject.

The list of the applications of these processes is of course too long to mention. However we shall mention a few. One application is in disease-epidemics, where the battle is between the infectives, the carriers of the disease-causative agent and the susceptibles. In 1964, Neyman and Scott [73] studied a stochastic model of the phenomenon underlying the disease epidemic, which takes into account the spacial movement of the infectives in the habitat, an important factor missing in most of the earlier models. However another important feature of their model is the extensive use of branching processes. Here the progeny of an infective are to be identified with the susceptibles getting infected by this infective during the time he remains infectious.

Another example where the branching processes are used is the extensive work of Karlin and McGregor [51] on genetic models, particularly the fixed size or the so called finite population models, similar to the ones originally introduced by Wright [100] in 1931 and Fisher [31] in 1930. At first sight it would appear inconvenient to study a fixed size population model while using branching processes, because the population size in these processes varies from generation to generation. However, it is possible to define a branching process conditioned on the presence of the same number of individuals in each generation. This resulted in what Karlin and McGregor call a <u>Direct Product branching process</u>. They used this approach to formulate among others, a

one-locus, two allele model of a finite population with the incorporation in the model of factors such as selection, mutation, migration and drift due to finite population size, etc. The reader may refer to Karlin [47], [48], for an expository account of these and other stochastic models in population genetics.

Among many situations, where the branching processes have been used as tools for theoretical investigations of other related processes, one situation arises in the study of the distribution of the length of a busy period in queueing theory. Here a branching process is observed as imbedded in an M/G/1 queue, as pointed out by Kendall [53]. The symbol M/G/1 stands here for a queueing system with a single server, in which customers arrive according to a homogeneous Poisson process and in which the service times are independent and identically distributed with an arbitrary common distribution. The imbedding of a branching process as explained by Kendall [53] goes as follows: Let the customer whose arrival initiates the busy period be called the 'ancestor'. This customer forms the zero-order generation corresponding to a G-W process. During his service time the new customers arriving, say X_1 in number, form the first generation. During their total service time, the further (new) customers arriving, say X_2 in number, constitute the second generation corresponding to a G-W process, and so on. Here the new customers arriving during the service time of a customer constitute the progeny of this customer. As it turns out in an M/G/1 queue, the random variables denoting the numbers of progeny for various customers (defined in this manner) are independent and identically distributed, a condition essential for X_n to be a G-W process. The busy period of course terminates as soon as this process or the 'family' becomes extinct. The length in time of a busy period is equal to the aggregate of the service times of all the individuals in various generations (including the ancestor) until the family becomes extinct. Thus the above interpretation

leads to a simple way of studying the busy period and some other properties of an M/G/1 queue, with the help of an already well developed G-W processes. The reader may refer to Neuts [70] for an investigation of M/G/1 queue along these lines.

Finally the reader may also refer to Harris [39], Bharucha-Reid [10], [11], Bartoszyński [5], Bühler [12] and Puri [78], for other applications of branching processes.

3 BIRTH AND DEATH PROCESSES. Another class of processes commonly arising in applications is the so called Birth and Death processes (B-D processes). These are nonnegative integer valued continuous time Markov processes. Some members of this class are also known to share properties of those of continuous time branching processes. Here the process after waiting for a random length of time in a given state jumps up by one step if there is a birth and down by one if there is a death. The birth and death events are of course also random events. Feller [22] was the first to study these processes extensively as early as 1939. These and his later contributions made far reaching impacts on the use and further investigations of these processes. Polya studied a pure time nonhomogeneous (i.e. the birth rates being time-dependent) birth process, now widely known as Polya process. Here the birth rates are both time as well as state-dependent. Bates and Neyman [7] also used the birth processes in connection with stochastic models on accident proneness, the history of which Professor Neyman himself has already touched in his presentation at this symposium. Kendall [52] gave a complete solution for the first time of a linear time nonhomogenous birth and death process. Lederman and Reuter [64] and later Karlin and McGregor [49], [50], made extensive studies of the spectral properties of the time-homogeneous B-D processes, which led to further insight into the behavior of these processes.

Practical situations where B-D processes arise are beyond enumeration. One such situation where these processes commonly arise are the queueing theory problems. Here a person leaving the queue after service is considered as a death, while a person arriving for service is considered as a birth. Again these processes have also been used extensively in developing stochastic models for carcinogenesis, see for instance, Neyman [71], Neyman and Scott [73] and Kendall [55]. Another situation, where a B-D process has been used as a model initially in the work of Steinberg and Stahl [95] and later by Gani [34], is the Bacteriophage Reproduction. The reader is referred to a detailed account of this work and of other authors in this area, appeared in a expository paper by Gani [35]. Some later work also appears in Puri [79]. Briefly the non-mathematical details are as follows:

The bacteriophage or a phage for short, is a virus which feeds and multiplies only in a bacterium. Gani was concerned with the so called T-bacteriophages. Such a phage in its mature form consists of a DNA strand enclosed in a protein head, and attached with it is a syringe type mechanism, which helps the phage to insert the DNA strand into the bacterium. After insersion the DNA strand, called the vegative phage, starts multiplying in the bacterium. Meanwhile the protein coatings and other parts necessary for the assembly of a mature phage are also under production. The bacterial own growth processes are of course considered stopped and it is considered as dying after infection. Soon some of the vegetative phages start turning into mature ones, after their assembly. The phages in their mature form are of course no longer capable of multiplying. Finally, after a random length of time from initial virus infection, the life of the bacterium ends with a burst, the so called Lysis, at which point it yields a random number of mature phages, which are then ready to infect other bacteria in the suspension medium and the phage parasitic cycle starts all over again. Here, since the mature phage is no longer capable of multiplying, Gani

treated the conversion of a vegatative phage to a mature one as a death, in his B-D process model of the above phenomenon. This is of course one of the many examples, where B-D processes have been used as part of the underlying mechanism in developing appropriate stochastic models. Again there is an extensive literature available on the discrete time analogs of B-D processes, the so called the Random Walk Models defined on integers. The reader may refer to an excellent treatise on this subject due to Spitzer [92].

4 EMIGRATION-IMMIGRATION PROCESSES. Another class of processes of considerable importance in biology goes under the name Emigration-Immigration Processes, and are extensively used in demographic models on population dynamics as the name suggests. However they appear elsewhere too. One of the early papers, which gave an impetus to further research in this area is due to Fix and Neyman [32] appeared in 1951, where they studied a stochastic model of recovery, relapse, death and loss of patients in connection with cancer. Since then many of Neyman's students and others have contributed to the study of such processes and in particular to their applications. In particular, the work of Chiang [13], [14], in connection with competing risks of illness and of death is worth mentioning. Here an individual is considered to be migrating from one state of illness to another or from life itself to death, and so forth.

5 SEMI-MARKOV PROCESSES. Most of the models mentioned in the previous two sections are so called Markovian in nature and in the time homogeneous case, this means that the random length of stay of the process in a given state before it moves to another state has an exponential distribution. Because of the well known lack of memory property of such distributions this means, for instance in the case of Emigration-Immigration processes, when you leave the present state you are in and where you go, does not depend on how long you

have already been in that state. In many diseases such an assumption appears unrealistic. For instance, in the case of a cancerous disease, the change of state of a person will depend more critically on how long he has had the growth. Weiss and Zelen [93] were led by these considerations, to the use of somewhat more general processes, the so called Semi-Markov Processes. Here the length of stay in a given state is assumed to have an arbitrary distribution not necessarily exponential. Such processes were originally introduced independently in 1954 by Lévy [65], [66] and Smith [90] and later in 1961 were extensively studied by Pyke [82], [83]. These processes are now finding more and more use in many live situations. For instance, Weiss and Zelen [99] as mentioned earlier have considered a semi-Markovian model and have applied it to the study of behavior of patients with Acute Leukemia. This I believe is a step in the right direction, and is most welcomed in so far as the applications of these processes in biology is concerned.

6 RENEWAL PROCESSES. Another class of processes, which may be considered as a special case of semi-Markov processes, is called the Renewal Processes. These processes have traditionally been used extensively in the areas of Life-testing and Reliability theory. In fact the name 'renewal theory' comes from problems in these areas, where one is concerned with the study of successive replacements (renewals) of items subject to failure. An item may be a machine, a light bulb, a vacuum tube, etc., which is replaced at the end of its lifetime by an item of the same kind. It is assumed that the lifetimes of items (all of the same kind) are independent and identically distributed random variables. Mathematically the renewal process $X(t)$ is defined as the number (counts) of renewals (failures) occurring during the interval $(0,t]$. An important special case where the common liftime distribution is exponential, is called the Poisson process, which in turn is also a special case of birth processes touched in Section 3. These processes have been used as models for the number of car accidents occurring

at an intersection, the number of telephone calls arriving at a telephone exchange, the number of immigrants arriving in a town, etc. Here the successive inter-arrival times of calls (or accidents) are to be identified with the lifetimes of the items mentioned earlier, while a call itself with a failure of an item.

Again if the time is measured in discrete units, one gets the so called discrete time renewal processes. These are also commonly known as <u>recurrent event process</u>, a term originally introduced by Feller, who is also credited for recognizing and studying these processes quite extensively (see Feller [23], [24], [28]).

The list of contributors to the theoretical study of renewal processes is long and it will suffice for the present to mention two references; the first is an expository paper due to Smith [91], who among others have extensively contributed to this area, and the other is a monograph due to Cox [16].

Again the Poisson processes have been extensively used for Modelling in Biology and Medicine; on the other hand their generalized version, namely the renewal processes have just started finding its proper place in their applications to these areas. A recent example is of their use in building models related to <u>neuron firing</u> (see Coleman and Gastwirth [15] and Hochman and Feinberg [42]).

<u>7 DIFFUSION PROCESSES</u>. Most of the processes mentioned so far, are such that the process X(t) takes discrete values usually over nonnegative integers, being a number or a count of something. However, there is another class of processes called the <u>Diffusion Processes</u>, where X(t) takes values on a continuous scale. For instance, in practical situations X(t) could be the amount of sugar or cholestrol in the blood at time t and so on. The difference between these processes and the ones, where X(t) takes discrete values, is basically the following:

In the discrete valued processes, the probability of a transition in a small interval of time Δt is small, but the size of the transition when it occurs is appreciable. For example, in a simple birth process the probability of a birth in interval Δt in a population of size n is a small quantity, but when a birth does occur, it adds a whole unit to the population. On the other hand, in diffusion processes where $X(t)$ is continuous valued, it is certain that some change will occur during interval Δt; however for small Δt this change will also be small.

Among others, Soviet mathematicians such as Dynkin [18] and U.S. mathematicians such as Feller [25], [26], [27] and Stone [96] and also Ito and McKean [46], have extensively contributed to the studies of these processes. One way, in which these processes arise often in biology, is the following:

Many problems in biology involve relatively large populations, subject to the transitions resulting from birth, death, mutation, infection (in epidemics), etc. When the population size is large, the transitions are relatively speaking small in size. However for a suitably chosen time scale, these transitions may be relatively frequent. Under these conditions it has been possible in many situations to use an approximate model of the diffusion type in which both the variable $X(t)$ and the time are continuous. This is analogous to the normal distribution approximation in Statistics used for the sum of a large number of small random variables. Among many, Feller [25], Kolmogorov [61] and Kimura [60] have used these processes extensively as suitable approximations to many live situations, arising particularly in genetics connected with gene-frequency.

8 QUANTAL RESPONSE PROCESSES. Another type of processes called the Quantal Response processes arise as follows. Consider the situations where $X(t)$ denotes the variable, such as, the number of disease causing organisms such as viruses or bacteria in the body of the host at time t, the size of the tumor

at time t, the number of tumors present at time t, or the amount of toxic drug present in the body of the host at time t, etc. In many live situations, associated with such a variable is a well defined response of the host called the quantal response, such as death of the host, burst of the cell, development of local lesion or some other detectable symptom. The host may be animal, egg membrane, tissue culture or a bacterium itself. The length of time T the host takes to respond starting from a convenient origin, is typically known as the response time and is a random quantity. In this connection it is usually convenient to introduce the so called <u>Quantal Response process</u> denoted by $Y(t)$, where $Y(t) = 1$ if the host has not responded by time t; $Y(t) = 0$ otherwise, so that the random variables $Y(t)$ and T are related as $P(T > t) = P(Y(t) = 1)$. Here one is concerned with the fundamental question as to the nature of connection between the quantal response process $Y(t)$ and the process $X(t)$ itself. Until about 1963, in many of the models concerned with the above situation, it was assumed that there exists a fixed threshold, same for each host, so that as soon as the process $X(t)$ touches this threshold, the host responds; i.e. the quantal response process $Y(t)$ changes its value from one to zero, an absorption state for the process $Y(t)$. Although there are few situations where such a hypothesis may appear reasonable such as the models for neuron-firing, however in many other live situations such a fixed threshold hypothesis does not appear to be strictly correct. Thus in [77], an alternative hypothesis originally suggested by LeCam, was adopted, namely, that the connection between the process $X(t)$ and the host's response is indeterministic in character. In other words, it is assumed that the value of $X(t)$, or of a random variable whose distribution is dependent on the process $\{X(t)\}$, determines not the presence or absence of response, but only the probability of response of the host. Here, unlike the model based on a threshold hypothesis, the state

of the process X(t) at the moment of the quantal response is a random quantity. The reader may refer for further details about the quantal response processes based on the nonthreshold hypothesis in Puri [77], [80]. Later similar nonthreshold assumptions were used in studying quantal response processes arising, in controlling a lethal growth process by Neuts [69], in bacteriophage reproduction by Puri [79], and more recently in developing a stochastic model for Rabies by Bartoszyński [6]. A third hypothesis also of the threshold type is often used for situations involving biological assays (see Finney [30]). Here each subject is assumed to have a threshold called its tolerance limit. Unlike the first threshold type model, this limit is assumed to vary from subject to subject in a random fashion over the population of subjects. However, in such cases this (tolerance) distribution is picked up typically on a rather adhoc basis. This and other objections led Puri and Senturia [81] to the consideration of models based on a nonthreshold hypothesis suitable for quantal response assays.

9 COMPETITION PROCESSES. Most of the processes mentioned thus far with the exception of the multi-type branching processes, involve a single population. Yet in many applications specially in biology, medicine and in ecology, one is confronted with processes involving two or more interacting populations. The problems here are relatively more challenging mathematically. These processes are typically called the Competition Processes. Some of the probabilistic aspects of these processes have been studied in some generality by Reuter [84] and Iglehart [43], [44]. More recently Kesten has studied the limit behavior of somewhat related processes falling in the present category, in a series of interesting papers ([57], [58], [59]). His work was inspired in part by the asymptotic behavior of certain branching processes and also the direct product branching processes introduced by Karlin and McGregor [51].

Historically models involving competitions between species, the so called Prey-Predator models, date back to Lotka [67] and Volterra [97] for their deterministic theories of struggle for existence. Extensive experimental work of Park [76] with flour-beetle Tribolium inspired further stochastic modelling in this area. The important paper of Neyman, Park and Scott [7] on 'Struggle for existence: The Tribolium model', needs a special mention. Here the competition between the two species of beetles is in part due to the fact that they eat each others' eggs and also their own, the so called Cannibalism.

Another area, where models of two or more interacting populations arise is the disease epidemics, where there is a continuing battle between the infectives (plus the carriers) and the susceptibles. Here the British researchers such as Bailey [2], Bartlett [3], [4], Kendall [54] and Gani [36], need a special mention.

Another situation, where competition processes appear in biology is the following: In certain disease processes initiated within the body of the host by the invading organisms, such as viruses or bacteria, the host is known to put up some kind of defense mechanism through entities such as antibodies. Here then the battle is between the infecting organisms and the antibodies with the host's life hanging in between. Unfortunately not many models have been considered in literature to cover such situations.

And finally, in essence, if I may add another example, our life itself is full of all kinds of competition and interacting processes and perhaps this is what makes life even more interesting.

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